

Remarks

Reconsideration of this application, as amended, is respectfully requested. A listing of all related patents and pending patent applications is attached as Appendix D.

As requested by the Examiner, the specification was amended to update the priority claim at page 1, lines 8-13. No new matter is added by this amendment.

Claims 237-265 were pending in this application. Claims 237, 238, 243, 252, and 253 are amended herein and new claims 433-441 are added. The amendments to claims 237 and 238 simply replace the term “conjugates” with “nanoparticles,” thereby making the entire claim set internally consistent. Similarly, claims 243 and 253 are amended merely by changing a plural term to a singular term, thereby improving the grammar of the claims. Moreover, claim 252 is amended simply to correct a typographical error. Support for the new claims can be found in the specification as originally filed. For instance, see Example 5 (page 90); Example 7 (page 95); and Example 19 (page 131, line 37 to page 136, line 16) in the specification. Accordingly, the amendments to claims 237, 238, 243, 252, and 253 and the addition of new claims 433-441 do not add new matter to the application. Claims 237-265 and 433-441 are now pending in this application.

The Examiner indicated that the Information Disclosure Statement (“IDS” filed 2/19/02 fails to comply with 37 CFR 1.98(a)(2), which requires that a legible copy of patent, publication or other information listed. However, the attached return post-card bears a Patent Office stamp indicating that the references cited in the IDS was in fact received by the Patent Office. However, a second set of IDS references was hand delivered to the Examiner under separate cover. The Applicants request that the Examiner return a copy of the executed PTO 1449 forms for all seven statements that were filed for this case.

Turning now to the Office action, claims 237-265 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite; claims 237, 241-243, 251-253, and 264-265 were objected to for obviousness-type double patenting over claims 1, 3, and 4 of U.S. Patent No. 6,417,340 (the ‘340 patent); claims 237-265 were rejected under § 102(e) as being anticipated by the ‘340 patent; claims 237, 241-244, 251-255, 264, and 265 were rejected § 102(e) as being anticipated by U.S. Patent No. 5,728,590 (“Powell”); and claims 237, 241-244, 251-255, 264, and 265 were

rejected § 102(e) as being anticipated by U.S. Patent No. 6,121,425 (“Hainfeld”). The Applicants respectfully traverse these rejections and objection.

a. Claim Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 237-265 under 35 U.S.C. § 112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. The Applicants respectfully traverse this rejection.

First, the Office stated that “the limitations in claims 237, 243 and 253 are unclear,” alleging that the claims “recite the limitations of the compositions in passive language.” The Applicants respectfully submit that this rejection is moot on light of the present amendment to the claims to correct for form. Second, the Office noted that claim 252 is indefinite because the limitation “the method” lacks antecedent basis. In response, the Applicants respectfully submit that this rejection is moot in light of the present amendment to the claim to correct for an obvious typographical error.

Third, the Office rejected claim 244 because the limitations “it” and “spacer portion” are allegedly unclear. More particularly, the Examiner stated that it was unclear whether “it” “refers to the spacer portion of the nanoparticle or the spacer portion of the recognition oligonucleotide” and whether “spacer portion” “refers to the recognition oligonucleotide or the nanoparticle.” The Applicants respectfully traverse this rejection. With respect to the term “spacer portion,” please note that spacer portion is used in only one way in claim 243, from which claim 244 depends: “each of the recognition oligonucleotides comprising a spacer portion.” Claim 243 thus makes clear that the spacer portion is included in the recognition oligonucleotide. This being so, it is clear that the term “it” in claim 244 also refers to the spacer portion of the recognition oligonucleotide. See the originally filed specification at page 79, line 11 to page 80, line 7.

In light of the above discussion, the Applicants submit that withdrawal of the section 112, first paragraph, rejection against claims 237-265 is in order and is respectfully requested.

b. Obviousness-type Double Patenting Rejection under 35 U.S.C. section 103

The Patent Office rejected claims 237, 241-243, 251-253, and 264-265 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, and 4 of U.S. Patent No. 6,417,340 B1. Claims 1, 3 and 4 of the ‘340 patent are

directed specifically to aggregated nanoparticle probes while the instant composition claims are directed to a nanoparticle having oligonucleotides bound thereto, both which are different types of probes. In comparing the language between the cited claims of the '340 patent and the instant cited claims, the Applicants do not believe that the nanoparticle-oligonucleotide conjugate probes of the instant claims are obvious in view of the aggregate probes of the '340 patent and that the instant claims are patently distinct. For instance, the instant claims have language calling for a particular surface density (e.g., claim 237) or for certain oligonucleotides (e.g., claim 243) which are not obvious in view of the claims in the '340 patent. For at least this reason, the Applicants respectfully submit that the withdrawal of the obviousness-type double patenting rejection against claims 237, 241-243, 251-253, 264, and 265 is in order and is respectfully requested.

c. Claim Rejections under 35 U.S.C. § 102(e)

The Patent Office stated that the changes made to § 102(e) by the AIPA of 1999 "do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000" The Applicants respectfully point out that the recent changes made to § 102(e) by AIPA do in fact apply to all pending applications. The Applicants submit that the three U.S. Patents cited by the Examiner to support a § 102(e) rejection are not prior art against the claims.

i. § 102(e) Rejection In View of Mirkin et al. (US 6,417,340)

The Patent Office rejected claims 237-265 under § 102(e) as being anticipated by Mirkin et al. U.S. Patent No. 6,417,340 ("the '340 patent"). The relevant portion of § 102(e) states: "A person shall be entitled to a patent unless—(e) the invention was described in— . . . a patent granted on an application for patent filed in the United States before the invention by the applicant for patent . . . by another ." In this case, the Mirkin patent issued from U.S. Patent application serial no. 09/693,352, filed October 20, 2000, which is a divisional of U.S. Patent application 09/344,667, filed June 25, 1999 (now U.S. Patent No. 6,361,944), which is a continuation-in-part of U.S. Patent application No. 09/240,755, filed Jan. 29, 1999 (abandoned) which is a CIP of PCT/US97/12783, filed July 21, 1997, claiming the benefit of a provisional application filed July 29, 1996. Meanwhile, the present application is a continuation of U.S. Patent No. 09/603,830, filed June 26, 2000 which is a CIP of U.S. Patent application no.

09/344,668, filed June 25, 1999 (now U.S. Patent No. 6,361,944), which is a continuation-in-part of U.S. Patent application No. 09/240,755, filed Jan. 29, 1999 (abandoned) which is a CIP of PCT/US97/12783, filed July 21, 1997, also claiming the benefit of a provisional application filed July 29, 1996. Since both the '340 patent and the instant application were derived from the same application (U.S.S.N. 09/344,667, now U.S. Patent No. 6,361,944) and ultimately claim the benefit of the same provisional application (60/031,809) filed July 29, 1996 (i.e., the present application and the Mirkin application belong to the same patent family and have the same earliest effective filing date), the '340 patent cannot be prior art under section 102(e) against the instant claims. Accordingly, the Applicants respectfully submit that the '340 patent is unavailable as prior art under § 102(e) against the present application. Withdrawal of the section 102(e) rejection of claims 237, 241-244, 251-255, 264, ad 265 based on the '340 patent is in order and is respectfully requested.

ii. § 102(e) Rejection In View of Powell et al. (US 5,728,590)

The Examiner rejected claims 237, 241-244, 251-255, and 264-265 under § 102(e) as being anticipated by Powell et al. U.S. Patent No. 5,728,590 ("Powell"). More particularly, the Examiner stated that the Powell patent "teaches nanoparticle-oligonucleotide conjugates that comprise oligonucleotides attached to nanoparticles," citing col. 14-16, lines 1-67; "metal nanoparticles that contain gold," citing col. 14, lines 35-52; and "that the spacer portion of the recognition oligonucleotide is covalently bound to a moiety . . .," citing col. 15, lines 1-24 in support. The Applicants respectfully traverse this rejection.

As a general rule, for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. Corning Glass Works v. Sumitomo Electric, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. Connell v. Sears, Roebuck & Co., 220 U.S.P.Q 193, 1098 (Fed. Cir. 1983). Applicants respectfully submit that Powell cannot be applied to support an anticipation rejection of the claims under 35 U.S.C. section 102(e).

The Applicants respectfully submit that Powell simply does not teach the claimed invention of the present application. In this application, there are three independent claims: 237, 243, and 253. Each of the independent claims is directed to "nanoparticles having

oligonucleotides attached to them” Moreover, each of the claims recite features that are not disclosed by Powell. For instance, claim 237 is directed to nanoparticles wherein the oligonucleotides are “present on surface of the nanoparticles at a surface density sufficient so that the nanoparticles are stable;” claim 243 is directed to nanoparticles wherein “each of the recognition oligonucleotides compris[es] a spacer portion and a recognition portion . . . ;” and claim 253 is directed to nanoparticles comprising “at least one type of recognition oligonucleotide . . . and a type of diluent oligonucleotide.”

By contrast, Powell focuses on the incorporation of metallic clusters into dyes (e.g., see Examples 1-3, 7-10, and 20-35) and proteins (e.g., see Examples 4-6 and 11-19). Powell contains only vague statements regarding the incorporation of metallic clusters into nucleic acids and provides only a single example (Example 36). For instance, at column 4, lines 2-5, Powell teaches: “The organometallic particles may be attached to antitumor antibodies, or other targeting materials such as peptides, nucleic acids, or hormones, and used for sensitive diagnosis in vitro or in vivo.” Similarly, at column 5, lines 57-59, Powell teaches: “Described herein are methods to incorporate organometallic particles into nucleic acids to provide extremely sensitive assays based upon hybridization.” While at column 13, line 61 through column 14, line 7, Powell teaches that the organometallic particles “may be covalently incorporated into nucleic acids by several techniques,” and proceeds to briefly describe four such techniques, this disclosure is not a disclosure of the invention as presently claimed. Accordingly, withdrawal of the section 102(e) rejection of claims 237, 241-244, 251-255, 264, and 265 based on Powell is in order and is respectfully requested.

The Applicants further submit that, with respect to newly added claims 433 -440, Powell does not disclose or suggest any nanoparticle probe whereby “in the presence of said nucleic acid targets and under hybridization conditions, the nanoparticles having oligonucleotides bound thereto form complexes with said nucleic acid targets, the resulting nanoparticle-nucleic acid target complexes having a sharp melting profile and an increased melting temperature, relative to a melting profile and a melting temperature of analogous complexes formed with said nucleic acid targets and an unlabeled or fluorophore-labeled oligonucleotides having a sequence identical to the oligonucleotides bound to the nanoparticles, to allow for selective discrimination of any nucleotide insertion, deletion, or mismatch in said nucleic acid targets.” See, for instance, present claim 433. Powell is completely silent with respect to any nanoparticle that is capable

for forming a complex with a target nucleic acid whereby the resulting complex has a sharp melting profile and increased melting temperature.

Lest the Examiner consider applying Powell to reject the claims as being unpatentable under 35 U.S.C. section 103, the Applicants respectfully submit that Powell does not suggest anywhere the presently claimed nanoparticle probes. The nanoparticle-labeled probes of the invention that form complexes with target nucleic acids and the resulting complexes have sharp melting profiles and increased melting temperatures, relative to analogous complexes with unlabeled or fluorescent probes and the target nucleic acid, which is both surprising and unexpected since this property allows for extraordinary discrimination between perfectly matched and mismatched nucleic acid targets relative to complexes including unlabeled or fluorophore-labeled oligonucleotides. For instance, as shown in Figure 12 and discussed in Example 5 (page 90 in the specification, nanoparticle labeled oligonucleotide probes were prepared and contacted with various target nucleic acids under stringent conditions. With fully matched targets, the complex produced a positive result (blue color); with targets having one mismatched base, no complex formation occurred with the probes. In Figure 35(b), dehybridization of nanoparticle – labeled targets from capture strands bound to a surface was much more sensitive to temperature than that of an analogous fluorophore-labeled targets with identical sequences (Figure 35(a)). In addition, Figure 36 shows images of model oligonucleotide arrays challenged with unlabeled synthetic target and fluorescent-labeled (Figure 36(a)) or nanoparticle-labeled (Figure 36(b)) probes. That Figure showed that arrays challenged with model target and nanoparticle labeled probes and stained with silver solution clearly exhibited highly selective hybridization to complementary array elements and that the selectivity of the nanoparticle-based arrays was higher than that of the fluorophore-indicated arrays. See also the specification at page 135, lines 12-28. Powell is completely silent with respect to any nanoparticle probes having the recited features of the present claims.

In summary, Powell simply does not teach or suggest “nanoparticles having oligonucleotides attached to them, the oligonucleotides being present on surface of the nanoparticles at a surface density sufficient so that the nanoparticles are stable” (claim 237), nanoparticles wherein “each of the recognition oligonucleotides compris[es] a spacer portion and a recognition portion” (claim 243), or nanoparticles comprising “at least one type of recognition oligonucleotide . . . and a type of diluent oligonucleotide.” Accordingly, the Applicants

respectfully submit that Powell does not teach each and every limitation of the present claims and therefore respectfully request withdrawal of the § 102(e) rejection.

iii. § 102(e) Rejection In View of Hainfeld et al. (US 6,121,425)

The Patent Office rejected claims 237, 241-244, 251-255, and 264-265 under § 102(e) as being anticipated by Hainfeld et al. U.S. Patent No. 6,121,425 (“the ‘425 patent”). The claims rejected by the Office are the same as those rejected in view of Powell. Moreover, the reasons provided for the rejection in view of Hainfeld are identical to the reasons for the rejection in view of Powell. The Applicants note that Hainfeld is simply a continuation-in-part of Powell, that the disclosures of Hainfeld and Powell are nearly identical, and that the Examiner has cited the same portions of each patent against the present application. Accordingly, the Applicants hereby respectfully traverse this rejection on the basis that the ‘425 patent for the similar reasons that the Applicants traversed the § 102(e) rejection in view of Powell (see section 6b., above).

Like Powell, the Applicants respectfully submit that Hainfeld simply does not teach the claimed invention of the present application. In this application, there are three independent claims: 237, 243, and 253. Each of the independent claims is directed to “nanoparticles having oligonucleotides attached to them” Moreover, each of the claims recite features that are not disclosed by Hainfeld. For instance, claim 237 is directed to nanoparticles wherein the oligonucleotides are “present on surface of the nanoparticles at a surface density sufficient so that the nanoparticles are stable;” claim 243 is directed to nanoparticles wherein “each of the recognition oligonucleotides compris[es] a spacer portion and a recognition portion . . . ;” and claim 253 is directed to nanoparticles comprising “at least one type of recognition oligonucleotide . . . and a type of diluent oligonucleotide.”

By contrast, Hainfeld focuses on the incorporation of metallic clusters into dyes (e.g., see Examples 1-3, 7-10, and 20-35) and proteins (e.g., see Examples 4-6 and 11-19). Hainfeld contains only vague statements regarding the incorporation of metallic clusters into nucleic acids and provides only a single example (Example 36). For instance, at column 4, lines 2-5, Powell teaches: “The organometallic particles may be attached to antitumor antibodies, or other targeting materials such as peptides, nucleic acids, or hormones, and used for sensitive diagnosis in vitro or in vivo.” Similarly, at column 5, lines 57-59, Hainfeld teaches: “Described herein are methods to incorporate organometallic particles into nucleic acids to provide extremely sensitive

assays based upon hybridization.” While at column 13, line 61 through column 14, line 7, Hainfeld teaches that the organometallic particles “may be covalently incorporated into nucleic acids by several techniques,” and proceeds to briefly describe four such techniques, this disclosure is not a disclosure of the invention as presently claimed. Accordingly, withdrawal of the section 102(e) rejection of claims 237, 241-244, 251-255, 264, and 265 based on Hainfeld is in order and is respectfully requested.

The Applicants’ further submit that, with respect to newly added claims 433 -440, Hainfeld does not disclose or suggest any nanoparticle probe whereby “in the presence of said nucleic acid targets and under hybridization conditions, the nanoparticles having oligonucleotides bound thereto form complexes with said nucleic acid targets, the resulting nanoparticle-nucleic acid target complexes having a sharp melting profile and an increased melting temperature, relative to a melting profile and a melting temperature of analogous complexes formed with said nucleic acid targets and an unlabeled or fluorophore-labeled oligonucleotides having a sequence identical to the oligonucleotides bound to the nanoparticles, to allow for selective discrimination of any nucleotide insertion, deletion, or mismatch in said nucleic acid targets.” See, for instance, present claim 433. Hainfeld is completely silent with respect to any nanoparticle that is capable for forming a complex with a target nucleic acid whereby the resulting complex has a sharp melting profile and increased melting temperature.

Lest the Examiner consider applying Hainfeld to reject the claims as being unpatentable under 35 U.S.C. section 103, the Applicants respectfully submit that Hainfeld does not suggest anywhere the presently claimed nanoparticle probes. The nanoparticle-labeled probes of the invention form complexes with target nucleic acids and the resulting complexes have sharp melting profiles and increased melting temperatures, relative to analogous complexes with unlabeled or fluorescent probes and the target nucleic acid, which is both surprising and unexpected since this property allows for extraordinary discrimination between perfectly matched and mismatched nucleic acid targets relative to complexes including unlabeled or fluorophore-labeled oligonucleotides. For instance, as shown in Figure 12 and discussed in Example 5 (page 90 in the specification, nanoparticle labeled oligonucleotide probes were prepared and contacted with various target nucleic acids under stringent conditions. With fully matched targets, the complex produced a positive result (blue color); with targets having one mismatched base, no complex formation occurred with the probes. In Figure 35(b),

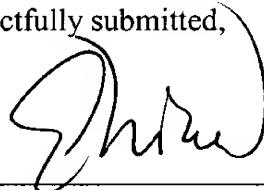
dehybridization of nanoparticle – labeled targets from capture strands bound to a surface was much more sensitive to temperature than that of an analogous fluorophore-labeled targets with identical sequences (Figure 35(a)). In addition, Figure 36 shows images of model oligonucleotide arrays challenged with unlabeled synthetic target and fluorescent-labeled (Figure 36(a)) or nanoparticle-labeled (Figure 36(b)) probes. That Figure showed that arrays challenged with model target and nanoparticle labeled probes and stained with silver solution clearly exhibited highly selective hybridization to complementary array elements and that the selectivity of the nanoparticle-based arrays was higher than that of the fluorophore-indicated arrays. See also the specification at page 135, lines 12-28. Hainfeld is completely silent with respect to any nanoparticle probes having the recited features of the present claims.

In summary, Hainfeld simply does not teach or suggest “nanoparticles having oligonucleotides attached to them, the oligonucleotides being present on surface of the nanoparticles at a surface density sufficient so that the nanoparticles are stable” (claim 237), nanoparticles wherein “each of the recognition oligonucleotides compris[es] a spacer portion and a recognition portion” (claim 243), or nanoparticles comprising “at least one type of recognition oligonucleotide . . . and a type of diluent oligonucleotide.” Accordingly, the Applicants respectfully submit that Hainfeld does not teach each and every limitation of the present claims and therefore respectfully request withdrawal of the § 102(e) rejection.

d. Conclusion

In view of the amendments and remarks above, the application is considered to be in good and proper form for allowance. Therefore, the Patent Office is respectfully requested to pass the application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of this application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Dated: February 19, 2003

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Appendix A: Marked-Up Version of Replacement Paragraph

1. Page 1, lines 8-13:

This application is a continuation of U.S. Patent Application No. 09/603,830, filed June 26, 2000 (now U.S. Patent No. 6,506,564), which is a continuation-in-part of [pending] U.S. Patent [a]Application [number] No. 09/344,667, filed June 25, 1999 (now U.S. Patent No. 6,361,944), which [was] is a continuation-in-part of [pending] U.S. Patent [a]Application [number] No. 09/240,755, filed January 29, 1999 (abandoned), which [was] is a continuation-in-part of [pending PCT application] PCT/US97/12783, [which was] filed July 21, 1997. Benefit of provisional applications numbers 60/031,809, filed July 29, 1996, and 60/200,161, filed April 26, 2000 is also hereby claimed.

Appendix B: Clean Version of the Pending Claims

B2
237. (Amended) Nanoparticles having oligonucleotides attached to them, the oligonucleotides being present on surface of the nanoparticles at a surface density sufficient so that the nanoparticles are stable, at least some of the oligonucleotides having a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide.

238. (Amended) The nanoparticles of Claim 237 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm².

239. The nanoparticles of Claim 238 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm².

240. The nanoparticles of Claim 239 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm² to about 40 picomoles/cm².

241. The nanoparticles of Claim 237 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

242. The nanoparticles of Claim 241 wherein the nanoparticles are gold nanoparticles.

B3
243. (Amended) Nanoparticles having oligonucleotides attached to them, the oligonucleotides comprising at least one type of recognition oligonucleotide, each of the recognition oligonucleotides comprising a spacer portion and a recognition portion, the spacer portion being designed so that it is bound to the nanoparticles, the recognition portion having a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide.

244. The nanoparticles of Claim 243 wherein the spacer portion has a moiety covalently bound to it, the moiety comprising a functional group through which the spacer portion is bound to the nanoparticles.

245. The nanoparticles of Claim 243 wherein the spacer portion comprises at least about 10 nucleotides.

246. The nanoparticles of Claim 245 wherein the spacer portion comprises from about 10 to about 30 nucleotides.

247. The nanoparticles of Claim 243 wherein the bases of the nucleotides of the spacer portion are all adenines, all thymines, all cytosines, all uracils or all guanines.

248. The nanoparticles of Claim 243 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm².

249. The nanoparticles of Claim 248 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm².

250. The nanoparticles of Claim 249 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm² to about 40 picomoles/cm².

251. The nanoparticles of Claim 243 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

252. (Amended) The nanoparticles of Claim 251 wherein the nanoparticles are gold nanoparticles.

B4
253. (Amended) Nanoparticles having oligonucleotides attached to them, the oligonucleotides comprising:

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at least one type of recognition oligonucleotide, each of the types of recognition oligonucleotides comprising a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide; and
a type of diluent oligonucleotide.

254. The nanoparticles of Claim 253 wherein, each of the recognition oligonucleotides comprises a spacer portion and a recognition portion, the spacer portion being designed so that it is bound to the nanoparticles, the recognition portion having a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide.

255. The nanoparticles of Claim 254 wherein the spacer portion has a moiety covalently bound to it, the moiety comprising a functional group through which the spacer portion is bound to the nanoparticles.

256. The nanoparticles of Claim 254 wherein the spacer portion comprises at least about 10 nucleotides.

257. The nanoparticles of Claim 256 wherein the spacer portion comprises from about 10 to about 30 nucleotides.

258. The nanoparticles of Claim 254 wherein the bases of the nucleotides of the spacer portion are all adenines, all thymines, all cytosines, all uracils or all guanines.

259. The nanoparticles of Claim 253 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm².

260. The nanoparticles of Claim 259 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm².

261. The nanoparticles of Claim 260 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm² to about 40 picomoles/cm².

262. The nanoparticles of Claim 254 wherein the diluent oligonucleotides contain about the same number of nucleotides as are contained in the spacer portions of the recognition oligonucleotides.

263. The nanoparticles of Claim 262 wherein the sequence of the diluent oligonucleotides is the same as that of the spacer portions of the recognition oligonucleotides.

264. The nanoparticles of Claim 253 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

265. The nanoparticles of Claim 264 wherein the nanoparticles are gold nanoparticles.

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433. A nanoparticle having one or more types of oligonucleotides bound thereto, at least one type of oligonucleotides having a sequence that is complementary to at least a portion of a nucleic acid target, wherein in the presence of said nucleic acid target and under hybridization conditions, the nanoparticle having oligonucleotides bound thereto form a complex with said nucleic acid target, the nanoparticle-nucleic acid target complex having a sharp melting profile and an increased melting temperature, relative to a melting profile and a melting temperature of an analogous complex formed with said nucleic acid target and an unlabeled or fluorophore-labeled oligonucleotide having a sequence identical to the oligonucleotides bound to the nanoparticles, to allow for selective discrimination of any nucleotide insertion, deletion, or mismatch in said nucleic acid target.

434. The nanoparticle of Claim 433 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm².

435. The nanoparticle of Claim 433 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm².

436. The nanoparticle of Claim 433 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm² to about 40 picomoles/cm².

437. The nanoparticle of claim 433, wherein the nanoparticles are metallic nanoparticles, semiconductor nanoparticles, or a combination thereof.

*B5
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438. The nanoparticle of Claim 433, wherein the nanoparticles are made of a noble metal.

439. The nanoparticle of Claim 438, wherein the nanoparticles are made of gold.

440. The nanoparticle of Claim 433, wherein the oligonucleotides, nanoparticles, or both bear functional groups for attachment of the oligonucleotides to the nanoparticles.

441. The nanoparticle of Claim 433, wherein the selective discrimination of said nucleotide insertion, deletion or mismatch in said nucleic acid target occurs under stringent hybridization conditions that are higher than those possible for said analogous complexes.

Appendix C: Rewritten Claims With Markings to Show Changes Made

237. (Amended) [Nanoparticle-oligonucleotide conjugates which are n]Nanoparticles having oligonucleotides attached to them, the oligonucleotides being present on surface of the nanoparticles at a surface density sufficient so that the [conjugates] nanoparticles are stable, at least some of the oligonucleotides having a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide.

238. (Amended) The [conjugates] nanoparticles of Claim 237 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm².

243. (Amended) Nanoparticles having oligonucleotides attached to them, the oligonucleotides comprising at least one type of recognition oligonucleotide[s], each of the recognition oligonucleotides comprising a spacer portion and a recognition portion, the spacer portion being designed so that it is bound to the nanoparticles, the recognition portion having a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide.

252. (Amended) The [method] nanoparticles of Claim 251 wherein the nanoparticles are gold nanoparticles.

253. (Amended) Nanoparticles having oligonucleotides attached to them, the oligonucleotides comprising:

at least one type of recognition oligonucleotide[s], each of the types of recognition oligonucleotides comprising a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide; and
a type of diluent oligonucleotide[s].

- 433. A nanoparticle having one or more types of oligonucleotides bound thereto, at least one type of oligonucleotides having a sequence that is complementary to at least a portion of a nucleic acid target, wherein in the presence of said nucleic acid target and under hybridization conditions, the nanoparticle having oligonucleotides bound thereto form a complex with said nucleic acid target, the nanoparticle-nucleic acid target complex having a sharp melting profile and an increased melting temperature, relative to a melting profile and a melting temperature of an analogous complex formed with said nucleic acid target and an unlabeled or fluorophore-labeled oligonucleotide having a sequence identical to the oligonucleotides bound to the nanoparticles, to allow for selective discrimination of any nucleotide insertion, deletion, or mismatch in said nucleic acid target.

434. The nanoparticle of Claim 433 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm².

435. The nanoparticle of Claim 433 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm².

436. The nanoparticle of Claim 433 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm² to about 40 picomoles/cm².

437. The nanoparticle of claim 433, wherein the nanoparticles are metallic nanoparticles, semiconductor nanoparticles, or a combination thereof.

438. The nanoparticle of Claim 433, wherein the nanoparticles are made of a noble metal.

439. The nanoparticle of Claim 438, wherein the nanoparticles are made of gold.

440. The nanoparticle of Claim 433, wherein the oligonucleotides, nanoparticles, or both bear functional groups for attachment of the oligonucleotides to the nanoparticles.

441. The nanoparticle of Claim 433, wherein the selective discrimination of said nucleotide insertion, deletion or mismatch in said nucleic acid target occurs under stringent hybridization conditions that are higher than those possible for said analogous complexes.--

APPENDIX D

ATTY Case No.	Serial No./ Filing Date	Inventors/Title	Status
00-653-A	U.S. 09/927,777 Filed 8/10/01	Mirkin, Letsinger, Mucic, Storhoff, Elghanian, Taton, Garamella, Li, Park/ NANOPARTICLES HAVING OLIGONUCLEOTI DES ATTACHED THERETO AND USES THEREFORE	PENDING
00-713-B1	09/923,625 Filed 8/7/01	Mirkin, Letsinger, Mucic, Storhoff, Elghanian/ NANOPARTICLES HAVING OLIGONUCLEOTI DES ATTACHED THERETO AND USES THEREFOR	PENDING
00-713-C	09/344,667, filed 6/25/99	Mirkin, Letsinger, Mucic, Storhoff, Elghanian/ NANOPARTICLES HAVING OLIGONUCLEOTI DES ATTACHED THERETO AND USES THEREFORE	U.S. Patent No. 6,361,944, issued 3/26/02
00-713-I	U.S.S.N 09/603,830 Filed 6/26/00	Mirkin, Letsinger, Mucic, Storhoff, Elghanian, Taton; NANOPARTICLES HAVING OLIGONUCLEOTI DES ATTACHED THERETO AND USES THEREFOR	U.S. Patent No. 6,506,564, issued 1/14/03
00-713-I-1	09/961,949 9/20/01	Mirkin, Letsinger, Mucic, Storhoff, Elghanian, Taton;	ALLOWED

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ATTY Case No.	Serial No./ Filing Date	Inventors/Title	Status
		NANOPARTICLES HAVING OLIGONUCLEOTI DES ATTACHED THERETO AND USES THEREFOR	
00-713-I-2	09/957,318 9/20/01	See 00-713-I-1	PENDING
00-713-I-3	09/957,313 9/20/01	See 00-713-I-1	PENDING
00-713-I-4	09/966,491 9/28/01	See 00-713-I-1	PENDING
00-713-I-5	09/966,312 9/28/01	See 00-713-I-1	PENDING
00-713-I-6	09/967,409 9/28/01	See 00-713-I-1	PENDING
00-713-I-7	09/974,500 10/10/01	See 00-713-I-1	PENDING
00-713-I-8	09/974,007 10/10/01	See 00-713-I-1	PENDING
00-713-I-9	09/973,638 10/10/01	See 00-713-I-1	PENDING
00-713-I-10	09/973,788 10/10/01	See 00-713-I-1	PENDING
00-713-I-11	09/975,062 10/11/01	See 00-713-I-1	PENDING
00-713-I-12	09/975,376 10/11/01	See 00-713-I-1	PENDING
00-713-I-13	09/975,384 10/11/01	See 00-713-I-1	PENDING
00-713-I-14	09/975,498 10/11/01	See 00-713-I-1	PENDING

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00-713-I-15	09/975,059 11/11/01	See 00-713-I-1	PENDING
00-713-I-16	09/976,601 10/12/01	See 00-713-I-1	PENDING
00-713-I-17	09/976,968 10/12/01	See 00-713-I-1	PENDING
00-713-I-18	09/976,971 10/12/01	See 00-713-I-1	PENDING
00-713-I-19	09/976,863 10/12/01	See 00-713-I-1	PENDING
00-713-I-20	09/976,577 10/12/01	See 00-713-I-1	PENDING
00-713-I-21	09/976,618 10/12/01	See 00-713-I-1	PENDING
00-713-I-22	09/981,344 10/15/01	See 00-713-I-1	PENDING
00-713-I-23	09/976,900 10/12/01	See 00-713-I-1	PENDING
00-713-I-24	09/976,617 10/12/01	See 00-713-I-1	PENDING
00-713-I-25	09/976,378 10/12/01	See 00-713-I-1	PENDING
00-713-L	U.S.S.N. 09/693,005 Filed 10/20/00	Mirkin, Letsinger, Mucic, Storhoff, Elghanian/ NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREFORE	U.S. Patent No. 6,495,324, issued 12/17/02
00-713-M	U.S.S.N.	Mirkin, Letsinger,	U.S. Patent No.

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	09/693,352 Filed 10/20/00	Mucic, Storhoff, Elghanian/ NANOPARTICLES HAVING OLIGONUCLEOTI DES ATTACHED THERETO AND USES THEREFORE	6,417,340, issued 7/9/02
00-714-G	U.S. 09/830,620 Filed 8/15/01	Mirkin, Nguyen/ NANOPARTICLES WITH POLYMER SHELLS	PENDING
00-715-A	U.S. 09/760,500 Filed 1/12/01	Mirkin, Letsinger, Mucic, Storhoff, Elghanian, Taton; Garamella, Li/ METHOD OF ATTACHING OLIGONUCLEOTI DES TO NANOPARTICLES AND PRODUCTS PRODUCED THEREBY	PENDING
00-1085-A	U.S.S.N. 09/820,279 Filed 3/28/01	Mirkin, Letsinger, etc./ METHOD AND MATERIALS FOR ASSAYING BIOLOGICAL MATERIALS	PENDING
00-1086-A	U.S. 09/903,461 Filed 7/11/01	Letsinger, Garimella/ METHOD OF DETECTION BY ENHANCEMENT OF SILVER STAINING	PENDING
01-565-A	USSN 10/125,194 Filed 4/18/02	Mirkin, Nguyen, Watson, Park/ OLIGONUCLEOTI DE-MODIFIED ROMP POLYMERS AND CO- POLYMERS	PENDING
01-599-A	U.S.S.N.	Storhoff/NOVEL	PENDING

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	10/291,291 Filed 11/08/02	THIOL-BASED METHOD FOR ATTACHING OLIGONUCLEOTI DES TO NANOPARTICLES	
01-661-A	U.S.S.N. 10/034,451 Filed 12/28/01	Mirkin, Cao, Jin/ DNA-MODIFIED CORE-SHELL AG/AU NANOCRYSTALS	PENDING
01-661-C	U.S.S.N. 10/153,483 Filed 5/22/02	Mirkin, Cao, Jin/ DNA-MODIFIED CORE-SHELL AG/AU NANOCRYSTALS	PENDING
01-1565-A	U.S.S.N. 10/266,983 Filed 10/08/02	Park, Taton, Mirkin/ARRAY- BASED ELECTRICAL DETECTION OF DNA USING NANOPARTICLE PROBES	PENDING
01-1705-A	U.S.S.N. 10/108,211 Filed 3/27/02	Nam, Park, Mirkin/BIO- BARCODES BASED ON OLIGONUCLEOTI DE-MODIFIED NANOPARTICLES	PENDING
02-338-B	USSN 10/172,428 Filed 6/14/02	Cao, Jin, Nam, Mirkin/MULTICHA NNEL DETECTION USING NANOPARTICLE PROBES WITH RAMAN SPECTROSCOPIC FINGERPRINTS	PENDING